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ORIGINAL RESEARCH

Association of Cardiovascular Risk Burden With Risk and Progression of Disability: Mediating Role of Cardiovascular Disease and Cognitive Decline

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BACKGROUND: Cardiovascular risk burden has been linked to cardiovascular disease (CVD) and cognitive decline, but its association with disability is unclear. We aimed to examined the association of cardiovascular risk burden assessed by the Framingham general cardiovascular risk score (FGCRS) with the risk and progression of disability and estimated the extent to which CVD and cognitive decline mediate this association.

METHODS AND RESULTS: A total of 1480 older adults with no disabilities (mean age=79.32±7.38 years) from the Rush Memory and Aging Project were followed for up to 21 years. FGCRS at baseline was calculated and categorized into tertiles. Disability was assessed annually with activities of daily living. The number of CVDs was calculated by summing up the CVD events. Global cognitive function was assessed annually with a battery of 19 tests. Data were analyzed using the Cox model, linear mixed effects model, and mediation analysis. At the end of the follow-up, 713 (48.2%) participants developed disability. Compared with the lowest tertile of the FGCRS, the multiadjusted hazards ratios of disability were 1.34 (95% CI, 1.11–1.62) for the highest tertile. In addition, the highest FGCRS was associated with a change in activities of daily living score over time (β=0.057; 95% CI, 0.021–0.093). The association between FGCRS and change in activities of daily living was 13.8% mediated by the accumulation of CVDs and 25.1% by cognitive decline, respectively.

CONCLUSIONS: Higher cardiovascular risk burden increased the risk of disability and accelerated its progression over time. CVD accumulation and cognitive decline may partially mediate the association.

Key Words: cardiovascular disease ■ cognitive decline ■ cohort study ■ disability ■ Framingham general cardiovascular risk score

The world's population is aging. According to the World Health Organization, the world's population aged 60 years or older will be >2 billion by 2050.[1] Disability has posed a tremendous burden on our aging society. As the risk of disability increases with age, the occurrence of disability is expected to increase dramatically. Therefore, identifying risk factors for disability is important to develop prevention strategies to slow down the progression of disability.

Previous research has shown that individual cardiovascular risk factors such as smoking, hypertension, unfavorable lipid profile, and diabetes mellitus were associated with an increased risk of disability[2–5] or accelerated progression of disability[6] in older

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CLINICAL PERSPECTIVE

What Is New?

- Higher cardiovascular risk burden assessed by the Framingham general cardiovascular risk score is not only associated with an elevated risk of disability but also accelerates its progression over time.
- Cardiovascular disease accumulation and cognitive decline partially mediate the association between cardiovascular risk burden and disability progression.

What Are the Clinical Implications?

- Our findings highlight the importance of the control of cardiovascular risk for the prevention of both cardiovascular disease and cognitive decline, aiming at delaying the onset of disability and slowing down its progression among elderly people.
- Our study provides the first evidence on the mediating role of cardiovascular disease and cognitive decline in the development of disability related to vascular risk burden and thus may advance our understanding of potential mechanisms linking cardiovascular risk burden and disability.

Nonstandard Abbreviations and Acronyms

ADL	activities of daily living
BMI	body mass index
CVD	cardiovascular disease
FGCRS	Framingham General Cardiovascular Risk Score
HDL	high-density lipoprotein
IADL	instrumental activities of daily living

age. Meanwhile, accumulating evidence indicates that some cardiovascular risk factors tend to cluster among older adults.[7,8] The Framingham general cardiovascular risk score (FGCRS) is a prediction algorithm used to estimate the global cardiovascular risk burden in the general population.[9] Information on age, sex, total cholesterol, high-density lipoprotein (HDL) cholesterol, systolic blood pressure, antihypertensive medication use, current smoking, and diabetes mellitus status is included to calculate the absolute risk of a cardiovascular disease (CVD) event in individuals. So far, only one cross-sectional study showed a positive association between FGCRS and incident disability.[10] However, no community-based cohort studies to our knowledge have addressed the impact of vascular risk burden on the risk and progression of disability.

Many studies have documented an increased risk of CVD[9,11] and cognitive decline[12–14] among people with higher FGCRS. It has also been shown that CVD[15,16] and cognitive decline[17] accelerate the progression of disability in older adults. There are unanswered questions about CVDs and cognitive decline mediating the association between FGCRS and disability.

In the present study, we aimed to verify the hypothesis that higher FGCRS was associated with an increased risk of disability and a faster speed of disability progression and to assess the mediating roles of CVD accumulation and cognitive decline in the association between FGCRS and disability progression using data from a community-based cohort study of older adults with annual follow-up.

METHODS

The data supporting the findings of this study are available from MAP (Rush Memory and Aging Project). Researchers who are interested can contact the Rush Alzheimer's Disease Center to access data and study materials. Additional details about the data can be found on the Rush Alzheimer's Disease Center Resource Sharing Hub at https://www.radc.rush.edu.

Study Population

The study population was derived from MAP, an ongoing longitudinal study that investigates risk factors for common chronic neurodegenerative conditions in old age.[18] Details regarding the MAP study design and the evaluation protocol have been provided previously.[19] In brief, participants were recruited primarily from retirement communities, church groups, and senior centers throughout the greater Chicago area. At the time of enrollment and thereafter, each participant underwent a uniform structured clinical evaluation, including medical history, neurological examination, and detailed cognitive function testing.[18] Data on demographic characteristics, socioeconomic status, lifestyle factors, and anthropometrics (such as weight and height) were also collected at baseline and each visit.

Since 1997, a total of 2155 participants were annually followed for up to 21 years. Of the total participants, 675 were excluded because of disability at study entry (n=265), missing data on FGCRS (n=269), or missing data on activities of daily living (ADL) at follow-up (n=141). Thus, 1480 participants were available for the current study (Figure S1).

The study was approved by the institutional review board of Rush University Medical Center. All participants signed an informed consent and a repository consent that allowed their data to be shared after a detailed presentation of the risks and benefits associated with study participation.

Demographic Data

Education was recorded as maximum years of formal schooling (up to 30 years) at initial cognitive testing. Smoking was categorized as never smoker, former smoker, and current smoker at baseline. Alcohol consumption was defined as average grams of alcohol consumed per day in the past year.[20] Physical activity was measured by the sum of hours per week that the participant engaged in activities with using questions adapted from the National Health Interview Survey.[21] Weight and height were measured and recorded by a train technician blinded to previously collected data. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared (kg/m^2).[20] Depressive symptoms were assessed with a modified, 10-item version of the Center for Epidemiologic Studies Depression Scale.[22]

Assessment of FGCRS

The FGCRS was calculated at baseline based on information of age, sex, smoking, total cholesterol, HDL, systolic blood pressure, antihypertensive treatment, and diabetes mellitus according to the Framingham prediction model for general cardiovascular risk (Tables S1 and S2).[9] Total cholesterol level and HDL cholesterol level were derived from blood samples with a lipid panel. Missing data on total cholesterol and HDL at baseline (n=242) were imputed using data within 5 years if the participants had no incident ADL disability. Systolic blood pressure was measured twice in the sitting position with a 5-minute interval with a mercury sphygmomanometer by trained research assistants.[23] The mean of the 2 values was recorded. Antihypertensive medication usage was ascertained through direct visual inspection of all containers of prescription and over-the-counter agents allowed for medication documentation. Diabetes mellitus was defined by any of the following criteria: hemoglobin A1c ≥6.5%, fasting plasma glucose ≥126 mg/dL, random blood glucose ≥200 mg/dL, history of diabetes mellitus, or the use of diabetes mellitus medication.[24] The points from all of these risk factors were added to obtain the FGCRS, and the score was further categorized into tertiles as the lowest, middle, and the highest. A higher FGCRS indicated a greater risk of cardiovascular events in the future.

Assessment of CVD

All participants were under surveillance for the development of CVD events. CVD was defined as a composite of stroke, congestive heart failure, and other heart diseases. Stroke event was diagnosed based on clinician review of self-reported questions, neurological exam (when available), and interview of participant. Information about congestive heart failure was obtained by asking participants the following question: Since your last interview, have you been told by a doctor, nurse, or therapist that you had congestive heart failure? Information about heart diseases was obtained by asking participants the following question: Since your last interview, have you been told by a doctor, nurse, or therapist that you had a heart attack or coronary, coronary thrombosis, coronary occlusion, or myocardial infarction? The number of CVDs was calculated by summing up the above CVD events (ranged 0–3).

Assessment of Global Cognitive Function

Cognitive function was assessed at each evaluation using a battery of 21 cognitive performance tests at baseline.[18] The Mini-Mental State Examination was only used to describe the cohort. A summary measure of global cognitive function was constructed by the scores on the following 19 tests: Word List Memory, Word List Recall, immediate and delayed recall of story A from Logical Memory and the East Boston Story, Word List Recognition, Boston Naming Test, Verbal Fluency, reading test, Digit Span Forward, Digit Span Backward, Digit Ordering, Symbol Digit Modalities Test, Number Comparison, 2 indexes from a modified version of the Stroop Neuropsychological Screening Test, Judgment of Line Orientation, and the Standard Progressive Matrices.

The *z* scores were created by converting raw scores from all the tests to using the mean and standard deviation and then were averaged to yield the composite scores for global cognitive function. The composite scores were created as missing if more than half of the *z* scores are missing.

Assessment of Disability

ADL is a composite measure of disability measured annually with the Katz Activities of Daily Living Scale,[25] a self-report measure including 6 activities (eating, bathing, dressing, toileting, transferring, and walking across a small room). The ADL score is the sum of the number of items for which participants report the need for help/assistance and ranges from 0 to 6, with higher scores indicating greater disability. Respondents reporting difficulty in 1 or more ADL were considered to have a disability. Instrumental ADL (IADL) is a composite measure of disability using a sum of 8 items adapted from the Duke Older Americans Resources and Services project. IADL is only used as a covariate because almost half of the participants had an IADL disability at baseline.

Statistical Analysis

Differences of characteristics among the 3 groups of participants with the lowest, middle, and highest

FGCRS were evaluated using 1-way analysis of variance or the Kruskal–Wallis test for continuous variables and chi-square tests for categorical variables.

The Cox regression model was used to calculate the hazard ratios (HRs) with 95% CIs for the association of FGCRS with disability. The proportional hazards assumption was tested when the Cox model was employed and no violation of the assumption was observed. Laplace regression model was used to estimate the 50th percentile difference in disability onset time in relation to FGCRS.

The linear mixed effects model was used to analyze the associations between cardiovascular risk burden (continuous and categorical FGCRS) and annual change in ADL score using follow-up time (years) as the time scale. The fixed effect included cardiovascular risk burden, follow-up time, and their interactions. The random effect included random intercept and slope, allowing the individual differences at baseline and across follow-up. An overall type III sum of squares *F* tests was also performed to determine whether that variable as a whole is associated with outcome.

To test and quantify the mediation effect of CVD accumulation and cognitive decline on the association between FGCRS at baseline and disability, mediation analysis was performed using the causal steps approach based on the influential work of Baron and Kenny.[26] To perform mediation analysis, it is necessary to test 3 pathways: step 1, the association of FGCRS with disability; step 2, the association of FGCRS with CVDs accumulation or cognitive decline; step 3, the association of CVDs accumulation or cognitive decline with disability, controlling for FGCRS. All pathways were tested using a linear mixed effects model. We used the first half of follow-up data on the mediators (ie, number of CVDs and global cognitive function) and the entire follow-up data on the outcome (ie, ADL score) to address the issue of temporality between the mediators and the outcome. Bootstrapping methods was used to estimate the 95% CI of indirect (mediated) effects. Mediation was confirmed if the bias-corrected 95% CI for the indirect effect did not include zero.[27]

The Cox regression model, linear mixed effect model, and mediation analysis were first adjusted for age, sex, and education and then additionally adjusted for potential confounders including BMI, alcohol consumption, physical activity, depressive symptoms, baseline IADL, baseline number of CVDs, and baseline global cognitive function.

In the sensitivity analysis, we repeated the aforementioned models removing age and sex from the potential confounders. In addition, we excluded 382 participants with dementia at baseline and during the follow-up period because several components of the FGCRS, CVD, and outcome were self-reported. We further repeated the analysis using IADL and ADL as a combined outcome for disability in 887 IADL-free and ADL-free participants.

A 2-tailed *P* value of <0.05 was considered statistically significant for each analysis. All analyses were performed with Stata SE, version 15.0 (Stata Corp LP., College Station, TX).

RESULTS

Characteristics of the Study Population

Of the 1480 participants (mean age, 79.32± 7.38 years), 1101 (74.39%) were women and 379 (25.61%) were men. Compared with participants who had the lowest FGCRS, those with the highest were more likely to be older and male, and have lower education, lower HDL, a lower Mini-Mental State Examination score, a lower global cognition score, lower alcohol consumption, lower physical activity, higher BMI, and higher systolic blood pressure, as well as more likely to have diabetes mellitus or CVD at baseline and develop disability during the follow-up (Table 1).

Association Between FGCRS and Incident Disability

During the follow-up (median, 5.90 years; interquartile range, 2.02–9.08 years, accounting for 7784.31 person-years), 713 developed disability. In multiadjusted Cox regression models, continuous FGCRS was dose-dependently associated with the risk of disability, and each point increase of the FGCRS was related to a 4% higher risk of disability. Compared with the lowest tertile of FGCRS, the HRs (95% CIs) of incident disability were 1.27 (1.05–1.53) for the middle tertile and 1.34 (1.11–1.62) for the highest tertile, respectively (Table 2).

Laplace regression analysis showed that the multiadjusted 50th percentile difference (95% CI) of time (years) at incident disability for the participants with the highest FGCRS was 1.14 (0.20–2.07) years earlier than those with the lowest. Each score increase in FGCRS led to a 0.18-year earlier onset of disability (Table 2).

Relationship Between FGCRS and ADL Change Over Time

In a multiadjusted mixed effect model where FGCRS was treated as a continuous variable, the ADL score increased by an average annual rate of 0.088 points (95% CI, 0.024–0.152; *P*=0.007) during the follow-up period. Each point increase in FGCRS was associated

Table 1. Characteristics of the Study Population by FGCRS Categories (n=1480)

Characteristic	FGCRS (in Tertiles)			
	Lowest n=572 (38.65%)	Middle n=438 (29.59%)	Highest n=470 (31.76%)	*P* Value
Baseline				
Age (y), mean±SD	77.17±8.36	80.49±6.42	80.84±6.25	<0.001
Female, n (%)	506 (88.46)	321 (73.29)	274 (58.30)	<0.001
Education (y), mean±SD	15.29±3.01	14.80±3.33	14.78±3.36	0.014
Alcohol consumption (g/d), median (IQR)	1.08 (0.00 to 6.96)	1.08 (0.00 to 7.15)	0.00 (0.00 to 6.04)	0.040
BMI (kg/m^2), mean±SD	26.39±4.89	27.14±5.40	28.13±4.89	<0.001
Physical activity (h/w), median (IQR)	3.00 (1.17 to 5.25)	2.75 (1.17 to 4.67)	2.33 (0.67 to 4.50)	0.004
Smoking status, n (%)				0.058
Never	332 (58.04)	270 (61.64)	271 (57.66)	
Ever smoker	232 (40.56)	158 (36.07)	180 (38.30)	
Current smoker	8 (1.40)	10 (2.28)	19 (4.04)	
Depressive symptoms, median (IQR)	0 (0 to 1)	0 (0 to 1)	0 (0 to 2)	0.309
TC (mg/dL), mean±SD	191.23±35.13	194.58±43.20	194.32±46.13	0.646
HDL (mg/dL), mean±SD	66.73±17.53	61.86±19.18	53.99±17.35	<0.001
SBP (mm Hg), mean±SD	122.81±12.63	135.35±14.35	147.73±16.65	<0.001
Diabetes mellitus, n (%)	21 (3.67)	34 (7.76)	139 (29.576)	<0.001
FGCRS, mean±SD	11.83±2.09	15.97±0.81	19.78±1.77	<0.001
CVD, n (%)	71 (12.41)	76 (17.35)	103 (21.91)	<0.001
MMSE, mean±SD	28.40±1.85	27.79±2.58	27.59±2.81	<0.001
Global cognition score, median (IQR)	0.28 (−0.11 to 0.59)	0.12 (−0.31 to 0.48)	0.07 (−0.39 to 0.40)	<0.001
During follow-up				
Follow-up time, median (IQR)	6.52 (3.00 to 9.87)	6.25 (3.00 to 10.05)	6.01 (3.02 to 9.04)	0.386
Incident disability, n (%)	236 (41.26)	230 (52.51)	247 (52.55)	<0.001

Missing data: body mass index=10. BMI indicates body mass index; CVD, cardiovascular disease; FGCRS, Framingham general cardiovascular risk score; HDL, high-density lipoprotein; IQR, interquartile range; MMSE, Mini-Mental State Examination; SBP, systolic blood pressure; and TC, total cholesterol.

with a faster annual increase in ADL score over time (β=0.006; 95% CI, 0.002–0.010; *P*=0.006). When FGCRS was used as tertiles, the highest FGCRS (β=0.057; 95% CI, 0.021–0.093; *P*=0.002), but not the middle (β=0.023; 95% CI, −0.013 to 0.060; *P*=0.206), was related to a faster increase in ADL score compared with the lowest FGCRS during the follow-up period (Table 3 and Figure 1).

The Mediating Role of Number of CVDs and Global Cognitive Function

The mediation analysis revealed that a higher baseline FGCRS was associated with a faster annual increase in ADL score (β=0.0033; 95% CI, 0.0019–0.0048; *P*<0.001). The association of FGCRS with annual ADL score was attenuated when the number of CVDs

Table 2. HRs, 95% CIs, and 50th PDs in Years of Incident Disability in Relation to FGCRS

FGCRS	No. Subjects	No. Cases	Cox Model		Laplace Regression	
			HR (95% CI)*	HR (95% CI)†	50th PDs (y) (95% CI)*	50th PDs (y) (95% CI)†
Continuous	1470	707	1.06 (1.03 to 1.08)	1.04 (1.02 to 1.06)	−0.27 (−0.37 to −0.17)	−0.18 (−0.26 to −0.09)
Categorical (tertiles)						
Lowest	569	235	Reference	Reference	Reference	Reference
Middle	436	228	1.36 (1.13 to 1.64)	1.27 (1.05 to 1.53)	−1.42 (−2.59 to −0.25)	−0.86 (−1.70 to −0.01)
Highest	465	244	1.55 (1.29 to 1.88)	1.34 (1.11 to 1.62)	−2.09 (−3.21 to −0.97)	−1.14 (−2.07 to −0.20)

Missing data: 10 for body mass index. FGCRS indicates Framingham General Cardiovascular Risk Score; HRs, hazard ratios; and PDs, percentile differences.
*Adjusted for age, sex, and education.
†Adjusted for age, sex, education, body mass index, alcohol consumption, physical activity, depressive symptoms, baseline instrumental activities of daily living, baseline number of cardiovascular diseases, and baseline global cognition function.

Table 3. β Coefficients and 95% CIs of the Association Between FGCRS and Changes in Activities of Daily Living Score Over Time: Results From Mixed Effect Model

FGCRS	Model 1* β (95% CIs)	Type III *F*	*P* Value	Model 2† β (95% CIs)	Type III *F*	*P* Value
Continuous	0.001 (−0.007 to 0.008)	0.06	0.809	−0.003 (−0.011 to 0.005)	0.56	0.454
Categorical		0.08	0.919		0.86	0.422
Lowest	Reference			Reference		
Middle	−0.013 (−0.077 to 0.051)			−0.025 (−0.090 to 0.040)		
Highest	−0.004 (−0.070 to 0.062)			−0.045 (−0.113 to 0.023)		
Continuous×time	0.006 (0.002 to 0.010)	7.46	0.006	0.006 (0.002 to 0.010)	7.44	0.006
Categorical×time		4.89	0.008		4.87	0.008
Lowest×time	Reference			Reference		
Middle×time	0.025 (−0.012 to 0.062)			0.023 (−0.013 to 0.060)		
Highest×time	0.058 (0.022 to 0.095)			0.057 (0.021 to 0.093)		

FGCRS indicates Framingham General Cardiovascular Risk Score.
*Adjusted for age, sex, and education.
†Adjusted for age, sex, education, body mass index, alcohol consumption, physical activity, depressive symptoms, baseline instrumental activities of daily living, baseline number of cardiovascular diseases, and baseline global cognitive function.

(β=0.0023; 95% CI, 0.0003–0.0044; *P*<0.05) and global cognitive function (β=0.0021; 95% CI, 0.0002–0.0040; *P*<0.05) were separately entered into models (Figure 2).

In the CVD–mediation analysis, after controlling for a range of potential confounders, CVD accumulation mediated ≈13.8% of the association between FGCRS and ADL, whereas in the cognitive function–mediation analysis, cognitive decline accounted for ≈25.1% of the total association (Table S3).

Supplementary Analysis

Similar results to those from the initial analyses were obtained when we removed age and sex from the models (Tables S4 and S5, Figure S2) and when we excluded 382 participants with dementia at baseline and during the follow-up period (Tables S6 and S7, Figure S3). We further repeated the analysis using IADL and ADL as a combined outcome for disability in 887 IADL-free and ADL-free participants, which showed the results were similar to those from the initial analysis (Tables S8 and S9, Figure S4).

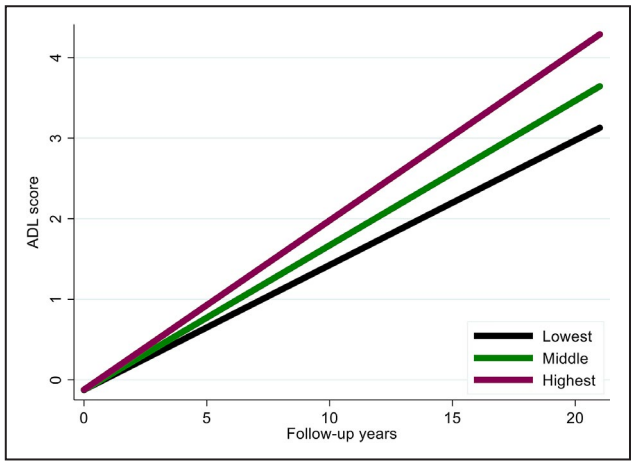

Figure 1. Average annual changes in ADL score according to tertiles of Framingham General Cardiovascular Risk Score. Model was adjusted for age, sex, education, body mass index, alcohol consumption, depressive symptoms, physical activity, baseline instrumental activities of daily living, baseline number of cardiovascular diseases, and baseline global cognitive function. ADL indicates activities of daily living.

DISCUSSION

In this community-based cohort study of older adults with yearly follow-up, we found that (1) compared with the lowest FGCRS, the highest FGCRS increased the risk of disability and anticipated disability onset by more than 1 year; (2) the highest FGCRS further accelerated the progression of ADL; and (3) CVD accumulation (about 14%) and cognitive decline (about 25%) partially mediated the association between FGCRS and ADL progression.

The relationship between individual cardiovascular risk factors and disability has been well documented. Several longitudinal studies have shown that older age, female sex, higher systolic blood pressure, diabetes mellitus, current smokers, or adverse lipid profile were individually associated with an increased risk of disability[2–5,28–32] and a faster speed of disability progression.[6,33–36] Only a few studies have addressed the combined effect of different cardiovascular risk factors on disability. One study found that people with normal systolic/diastolic blood pressure, normal serum total cholesterol, healthy weight, no hypertension, no diabetes mellitus, and not currently smoking had the lowest risk of disability in older age.[37] Another study that examined the effect of comorbid cardiovascular risk factors (including

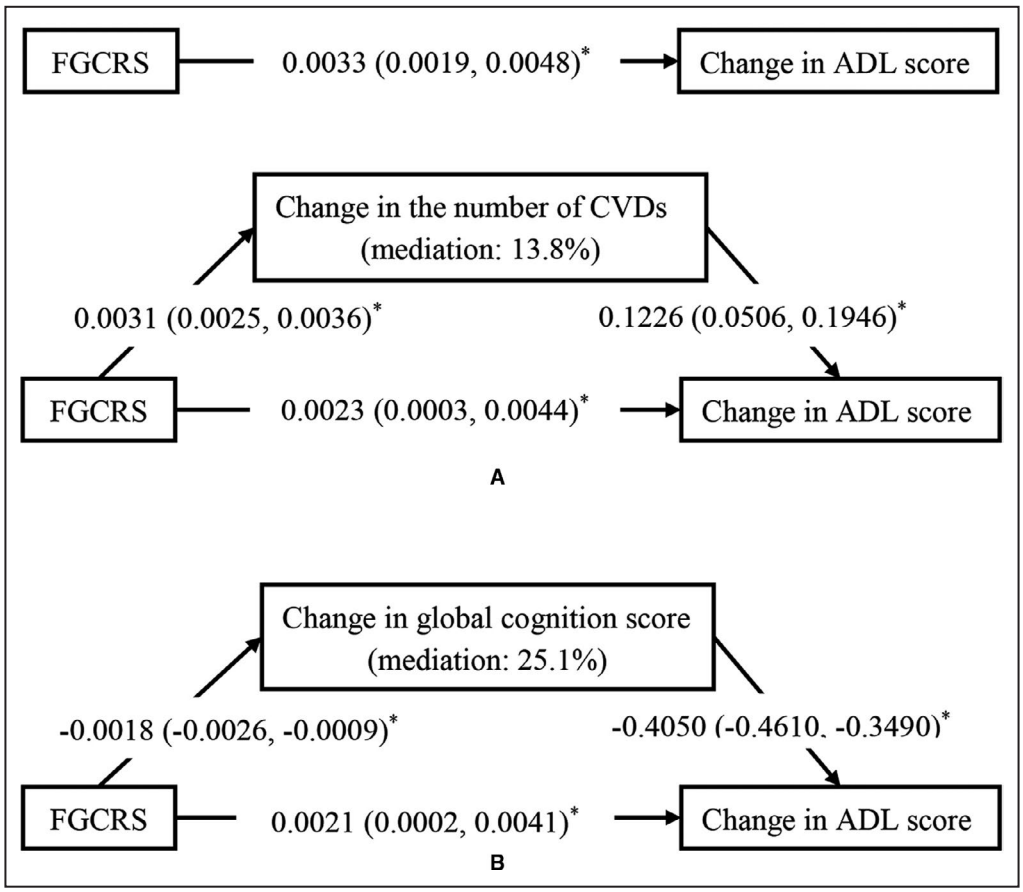

Figure 2. Mediating effects of changes in the number of CVDs (A) and global cognitive function (B) on the associations of FGCRS with ADL score changes.
Mediation model adjusted for age, sex, education, body mass index, alcohol consumption, physical activity, depressive symptoms, baseline instrumental activities of daily living, baseline number of cardiovascular diseases, and baseline global cognition function. ADL indicates activities of daily living; CVD, cardiovascular disease; and FGCRS, Framingham General Cardiovascular Risk Score. *P<0.05.

BMI, smoking, and physical activity) on the risk of disability (ADL) showed that people with higher cardiovascular risk had a greater number of disabilities than those with lower cardiovascular risk.[38] Only a cross-sectional study of patients with multiple sclerosis that used FGCRS indicated a positive correlation between FGCRS and disability.[10]

To our knowledge, no studies have evaluated the longitudinal association between FGCRS and risk of disability and its progression. In the current study, we found that highest FGCRS was associated with increased risk of disability and anticipated the onset of disability by more than 1 year compared with the lowest FGCRS. In addition, higher FGCRS was significantly accelerated the progression of ADL over time.

One type of the chain of risk model from the life course epidemiology is that 1 exposure not only has an independent effect on disease but also increases the risk of the subsequent exposure, which leads to outcome.[39] It has been well established that higher FGCRS could increase the risk of CVD[9,11] and accelerate cognitive decline.[12–14] Both conditions have been associated with an accelerated speed of disability progression.[15–17] However, to our knowledge no studies have so far evaluated the possible mediating role of CVD accumulation or cognitive decline in the in the association between FGCRS and disability trajectories. In the mediation analyses, we found that higher FGCRS was associated with an increased number of CVDs and cognitive decline, both of which were further related to the changes in ADL. Our results showed that an accumulation of CVDs and cognitive decline may partly mediate the association between FGCRS and disability progression. The proportion of the mediating effect by cognitive decline was greater than that by accumulation of CVDs. This may suggest that cognitive decline makes a greater contribution than physical depletion caused by CVD to the association of cardiovascular risk factors with the progression of disability.

Several mechanisms may account for the association between cardiovascular risk burden and the risk of disability. First, cardiovascular risk factors (eg, smoking, high cholesterol, and diabetes mellitus) are traditional risk factors for atherosclerosis, which is the primary cause of CVD.[40] CVD subsequently results in impairments in body systems (eg, coronary and systemic vasculature), which progress to functional limitations (eg, decrease in aerobic endurance and static functional impairment). As functional limitations accumulate and worsen, disability may develop.[41] Second, cardiovascular risk factors are associated with mixed brain lesions such as white matter hyperintensities and global and regional brain atrophy,[42] which are related to cognitive decline and dementia in older people.[43,44] Cognitive decline may lead to disability through limiting generic cognitive tasks such as remembering a list of words, reckoning, producing intelligible speech, managing interferences, or orientating oneself in time and space.[45] Apart from cognition and CVD, modifiable cardiovascular risk factors (eg, hypertension, BMI, and smoking) could increase the risk of peripheral neuropathy in patients with diabetes mellitus,[46] and patients with neuropathy are more likely to have difficulties with ADL.[47]

The strengths of this study include the use of a community-based cohort with an annual follow-up examination and relatively long follow-up. The outcome (ie, ADL score) and mediating variables (ie, number of CVDs and global cognition score) were examined at each wave. Furthermore, cardiovascular risk burden was assessed by using FGCRS. However, several limitations in this study should be pointed out. First, the generalizability of the findings is limited because the participants were recruited from a retirement house by a volunteer sampling process. Second, disability and CVD events were assessed based on retrospective self-report, which could be subject to recall bias. Third, participants were generally well educated and performed relatively well on cognitive tests, thus the observed association might have been underestimated. Finally, residual confounding, such as recruitment site, occupational characteristic, and trauma could not be completely ruled out, as information on those confounders was not available.

In conclusion, our study provides evidence that cardiovascular risk burden assessed by FGCRS is associated with the risk and progression of disability in old age. Accumulation of CVDs and cognitive decline may partially mediate the association of vascular risk burden with disability progression. Our findings highlight the importance of the control of cardiovascular risk for the prevention of both CVD and cognitive decline, aiming at delaying the onset of disability and slowing down its progression among elderly people.

ARTICLE INFORMATION

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Disclosures

None.

Supplementary Materials

Tables S1–S9
Figures S1–S4

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SUPPLEMENTAL MATERIAL

Table S1. Framingham General Cardiovascular Risk Score Calculating for Women.

Points	Age (years)	HDL (mg/dL)	TC (mg/dL)	SBP Not Treated (mmHg)	SBP Treated (mmHg)	Smoker	Diabetic
-3				<120			
-2		60+					
-1		50-59			<120		
0	30-34	45-49	<160	120-129		No	No
1		35-44	160-199	130-139			
2	35-39	<35		140-149	120-129		
3			200-239		130-139	Yes	
4	40-44		240-279	150-159			Yes
5	45-49		280+	160+	140-149		
6					150-159		

7	50-54	160+	
8	55-59		
9	60-64		
10	65-69		
11	70-74		
12	75+		
Points allotted			*Total*

HDL= High Density Lipoprotein, TC= Total Cholesterol, SBP=Systolic Blood Pressure.

Table S2. Framingham General Cardiovascular Risk Score Calculating for Men.

Points	Age (years)	HDL (mg/dL)	TC (mg/dL)	SBP Not Treated (mmHg)	SBP Treated (mmHg)	Smoker	Diabetic
-2		60+		<120			
-1		50-59					
0	30-34	45-49	<160	120-129	<120	No	No
1		35-44	160-199	130-139			
2	35-39	<35	200-239	140-159	120-129		
3			240-279	160+	130-139		Yes
4			280+		140-159	Yes	
5	40-44				160+		
6	45-49						
7							

8	50-54	
9		
10	55-59	
11	60-64	
12	65-69	
13		
14	70-74	
15	75+	
Points allotted		*Total*

HDL= High Density Lipoprotein, TC= Total Cholesterol, SBP=Systolic Blood Pressure.

Table S3. Mediating effects of changes in number of CVDs and global cognitive function in the association between Framingham General Cardiovascular Risk Score (FGCRS) and annual ADL score change, respectively.

	β	95% CI *	*P*
Mediator, number of CVDs			
FGCRS on mediator	0.0031	0.0025 to 0.0036	<0.001
Mediator on ADL score	0.1226	0.0506 to 0.1946	<0.001
Indirect effect of mediator†	0.0004	0.0001 to 0.0007	
Percent mediation	13.8%		
Mediator, global cognition score			
FGCRS on mediator	-0.0018	-0.0026 to -0.0009	<0.001
Mediator on ADL score	-0.4050	-0.4610 to -0.3490	<0.001
Indirect effect of mediator†	0.0007	0.0002 to 0.0012	
Percent mediation	25.1%		

* Adjusted for age, sex, education, BMI, alcohol consumption, physical activity, depressive symptoms, baseline instrumental activities of daily living, baseline number of cardiovascular diseases, baseline global cognition score.

† 95% confidence intervals for the indirect effect were calculated using bias-corrected bootstrapping.

CVD, cardiovascular disease; ADL, activities of daily living.

Table S4. Harzads ratios (HRs) and 95% CIs (confidence intervals) and 50th percentile differences (PDs) in years of incident disability in relation to Framingham General Cardiovascular Risk Score (FGCRS): resus from Cox model and Laplace repression.

FGCRS	No. subjects	No. cases	**Cox mode**	**Laplace repression**
			HR (95% CI) *	50th PDs (years) (95% CI) *
Continuous	1470	707	1.04 (1.02 to 1.06)	-0.20 (-0.31 to -0.09)
Categorical (tertiles)				
Lowest	569	235	Reference	Reference
Middle	436	228	1.29 (1.08 to 1.56)	-1.15 (-2.14 to -0.16)
Highest	465	244	1.31 (1.09 to 1.57)	-1.01 (-2.00 to -0.19)

*Adjusted for education, BMI, alcohol consumption, physical activity, depressive symptoms, baseline instrumental activities of daily living, baseline number of cardiovascular diseases, and baseline global cognition function.

FGCRS, Framingham General Cardiovascular Risk Score; HRs, hazard ratios; PD, percentile differences; CIs, confidence intervals.

Missing data: 10 for body mass index.

Table S5. β-coefficients and 95% confidence intervals (CIs) of the association between Framingham General Cardiovascular Risk Score (FGCRS) and changes in ADL score over time: results from Mixed effect model.

FGCRS	Model 1*		
	β (95% CIs)	Type III F	*P*
Continuous	-0.004 (-0.011 to 0.003)	1.18	0.277
Categorical		1.17	0.306
Lowest	Reference		
Middle	-0.031 (-0.095 to 0.032)		
Highest	-0.050 (-0.114 to 0.015)		
Continuous X time	0.006 (0.002 to 0.010)	7.43	0.006
Categorical X time		4.85	0.007
Lowest x time	Reference		
Middle x time	0.023 (-0.013 to 0.060)		
Highest x time	0.057 (0.021 to 0.093)		

*Adjusted for education, BMI, alcohol consumption, physical activity, depressive symptoms, baseline instrumental activities of daily living, baseline number of cardiovascular diseases, and baseline global cognitive function.

ADL, activities of daily living.

Table S6. Harzads ratios (HRs) and 95% CIs (confidence intervals) and 50th percentile differences (PDs) in years of incident disability in relation to Framingham General Cardiovascular Risk Score (FGCRS): resus from Cox model and Laplace repression.

FGCRS	No. subjects	No. cases	Cox model	Laplace repression
			HR (95% CI)*	50th PDs (years) (95% CI)*
Continuous	1089	409	1.04 (1.01 to 1.07)	-0.20 (-0.33 to -0.07)
Categorical (tertiles)				
Lowest	446	141	Reference	Reference
Middle	314	134	1.28 (1.00 to 1.64)	-1.05 (-2.11 to 0.01)
Highest	329	134	1.35 (1.05 to 1.74)	-1.37 (-2.46 to -0.28)

*Adjusted for age, sex, education, BMI, alcohol consumption, physical activity, depressive symptoms, baseline instrumental activities of daily living, baseline number of cardiovascular diseases, and baseline global cognition function.

FGCRS, Framingham General Cardiovascular Risk Score; HRs, hazard ratios; PD, percentile differences; CIs, confidence intervals.

Missing data: 9 for body mass index.

Table S7. β-coefficients and 95% confidence intervals (CIs) of the association between Framingham General Cardiovascular Risk Score (FGCRS) and changes in ADL score over time: results from Mixed effect model.

FGCRS	Model 1*		
	β (95% CIs)	Type III F	*P*
Continuous	-0.007 (-0.014 to -0.001)	4.48	0.035
Categorical		3.77	0.023
Lowest	Reference		
Middle	-0.058 (-0.113 to -0.003)		
Highest	-0.068 (-0.126 to -0.011)		
Continuous X time	0.004 (0.001 to 0.007)	5.13	0.023
Categorical X time		3.03	0.048
Lowest x time	Reference		
Middle x time	0.013 (-0.015 to 0.042)		
Highest x time	0.038 (0.010 to 0.066)		

*Adjusted for age, sex, education, BMI, alcohol consumption, physical activity, depressive symptoms, baseline instrumental activities of daily living, baseline number of cardiovascular diseases, and baseline global cognitive function.

ADL, activities of daily living.

Table S8. Harzads ratios (HRs) and 95% CIs (confidence intervals) and 50th percentile differences (PDs) in years of incident disability in relation to Framingham General Cardiovascular Risk Score (FGCRS): resus from Cox model and Laplace repression.

FGCRS	No. subjects	No. cases	**Cox model**	**Laplace repression**
			HR (95% CI)*	50th PDs (years) (95% CI)*
Continuous	885	633	1.04 (1.01 to 1.06)	-0.06 (-0.12 to 0.01)
Categorical (tertiles)				
Lowest	268	167	Reference	Reference
Middle	281	207	1.09 (0.88 to 1.35)	-0.46 (-1.24 to 0.32)
Highest	333	259	1.30 (1.04 to 1.61)	-0.44 (-1.18 to 0.30)

*Adjusted for age, sex, education, BMI, alcohol consumption, physical activity, depressive symptoms, baseline instrumental activities of daily living, baseline number of cardiovascular diseases, and baseline global cognition function.

FGCRS, Framingham General Cardiovascular Risk Score; HRs, hazard ratios; PD, percentile differences; CIs, confidence intervals.

Missing data: 5 for body mass index.

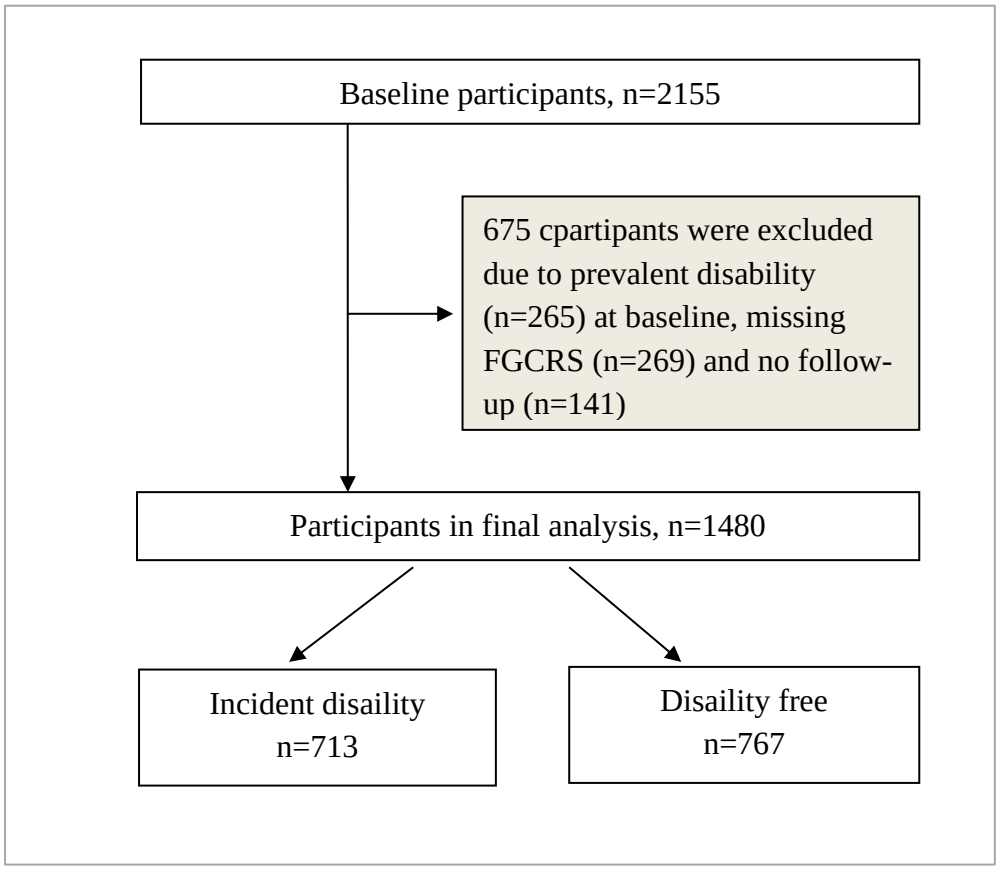
Table S9. β-coefficients and 95% confidence intervals (CIs) of the association between Framingham General Cardiovascular Risk Score (FGCRS) and changes in ADL score over time: results from Mixed effect model.

FGCRS	Model 1*		
	β (95% CIs)	Type III F	*P*
Continuous	-0.006 (-0.014 to 0.002)	1.99	0.158
Categorical		2.19	0.112
Lowest	Reference		
Middle	-0.052 (-0.122 to 0.017)		
Highest	-0.075 (-0.148 to -0.001)		
Continuous X time	0.005 (0.001 to 0.009)	7.14	0.008
Categorical X time		3.71	0.025
Lowest x time	Reference		
Middle x time	0.035 (0.001 to 0.070)		
Highest x time	0.045 (0.010 to 0.080)		

*Adjusted for age, sex, education, BMI, alcohol consumption, physical activity, depressive symptoms, baseline instrumental activities of daily living, baseline number of cardiovascular diseases, and baseline global cognitive function.

ADL, activities of daily living.

Figure S1. Flowchart of study participants.



FGCRS, Framingham General Cardiovascular Risk Score; ADL, activities of daily living.

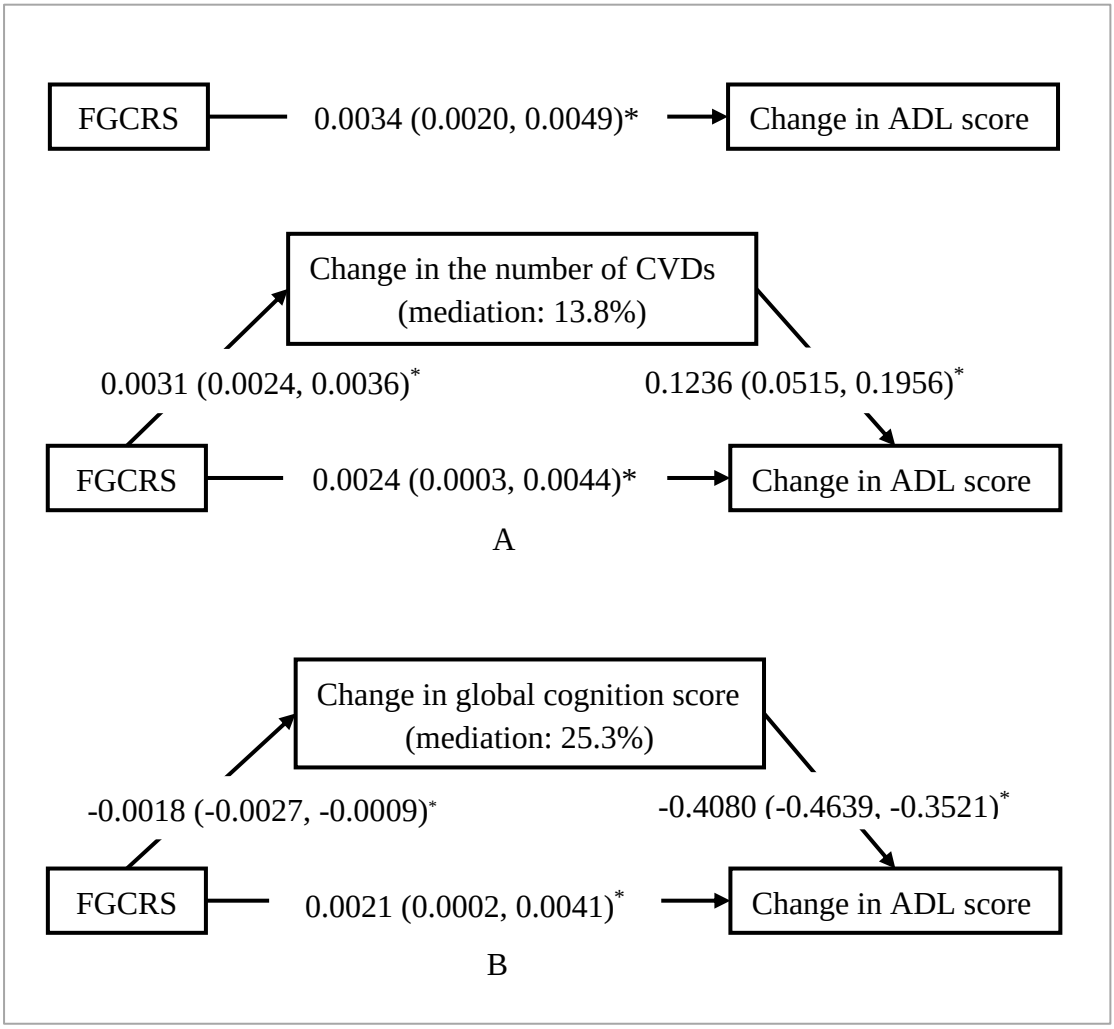


Figure S2. Mediating effects of changes in the number of CVDs (A), and global cognitive function (B) on the associations of Framingham General Cardiovascular Risk Score (FGCRS) with ADL score changes.

Mediation model adjusted for education, BMI, alcohol consumption, physical activity, depressive symptoms, baseline instrumental activities of daily living, baseline number of cardiovascular diseases, and baseline global cognition function.

*$p < 0.05$. CVD, cardiovascular disease; ADL, activities of daily living.

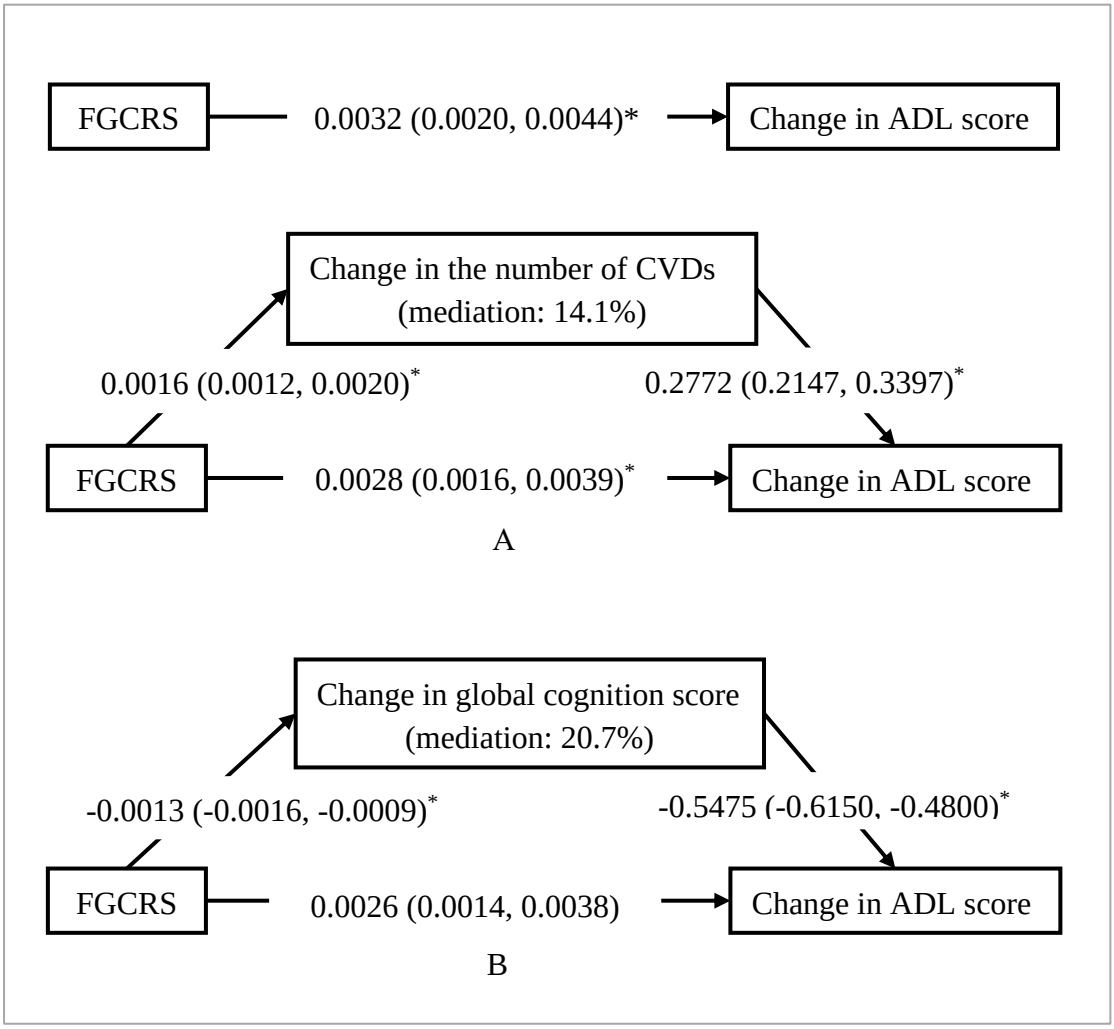


Figure S3. Mediating effects of changes in the number of CVDs (A), and global cognitive function (B) on the associations of Framingham General Cardiovascular Risk Score (FGCRS) with ADL score changes.

Mediation model adjusted for age, sex, education, BMI, alcohol consumption, physical activity, depressive symptoms, baseline instrumental activities of daily living, baseline number of cardiovascular diseases, and baseline global cognition function.

*$p < 0.05$. CVD, cardiovascular disease; ADL, activities of daily living.

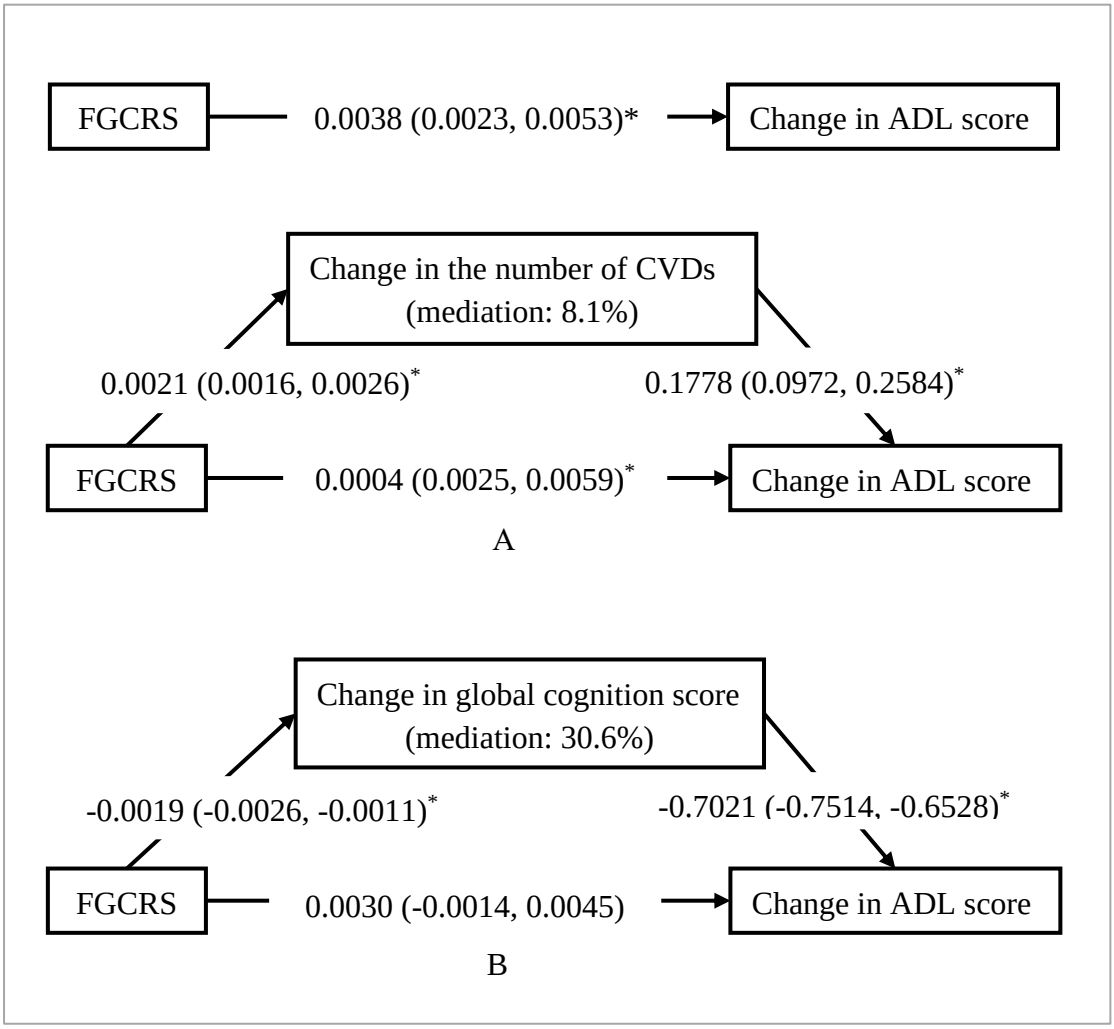


Figure S4. Mediating effects of changes in the number of CVDs (A), and global cognitive function (B) on the associations of Framingham General Cardiovascular Risk Score (FGCRS) with ADL score changes.

Mediation model adjusted for age, sex, education, BMI, alcohol consumption, physical activity, depressive symptoms, baseline instrumental activities of daily living, baseline number of cardiovascular diseases, and baseline global cognition function.

*$p < 0.05$. CVD, cardiovascular disease; ADL, activities of daily living.